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Chemokines orchestrate tumor cells and the microenvironment to achieve metastatic heterogeneity

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Abstract

Chemokines, a subfamily of the cell cytokines, are low molecular weight proteins known to induce chemotaxis in leukocytes in response to inflammatory and pathogenic signals. A plethora of literature demonstrates that chemokines and their receptors regulate tumor progression and metastasis. With these diverse functionalities, chemokines act as a fundamental link between the tumor cells and their microenvironment. Recent studies demonstrate that the biology of chemokines and their receptor in metastasis is complex as numerous chemokines are involved in regulating site-specific tumor growth and metastasis. Successful treatment of disseminated cancer is a significant challenge. The most crucial problem for treating metastatic cancer is developing therapy regimes capable of overcoming heterogeneity problems within primary tumors and among metastases and within metastases (intralesional). This heterogeneity of malignant tumor cells can be related to metastatic potential, response to chemotherapy or specific immunotherapy, and many other factors. In this review, we have emphasized the role of chemokines in the process of metastasis and metastatic heterogeneity. Individual chemokines may not express the full potential to address metastatic heterogeneity, but chemokine networks need exploration. Understanding the interplay between chemokine-chemokine receptor networks between the tumor cells and their microenvironment is a novel approach to overcome the problem of metastatic heterogeneity. Recent advances in the understanding of chemokine networks pave the way for developing a potential targeted therapeutic strategy to treat metastatic cancer.

Keywords

Chemokines/receptors; Heterogeneity; Angiogenesis; Epithelial-mesenchymal plasticity; Cancer stem cells; Therapy resistance

1 Introduction

Metastasis, defined as secondary cancer that spreads from its site of origin to another part of the body, is the primary cause of cancer-related deaths. Although the successful eradication

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Declarations

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of primary tumors is possible with surgery and the continuous improvements in adjuvant chemotherapy and radiotherapy, treating secondary cancer or metastases still presents itself as a significant challenge.

Improvements in cancer therapy require a rational understanding of every step of metastasis. One of the essential aspects of treating metastasis is to answer whether metastases result from random survivors of tumor cells or a representative of a selective subpopulation of tumor cells existing within the primary tumor population [1]. Only with the condition that metastasis is a selective process, the metastasized cells represent a group of tumor cells with specialized properties. The uniquely acquired properties by tumor cells during metastasis allow us to design therapies directed against it. The primary tumors and metastases are heterogeneous regarding response to different therapy regimes such as chemotherapy, specific immunotherapy, or radiotherapy. Hence, to develop novel anticancer agents, the response of both the primary tumor and secondary tumors should determine the efficacy of the anticancer agent.

In light of the recent metastasis studies, both tumor cell properties and host-tumor cell interactions can influence the metastatic process. Chemokines are among several factors that facilitate the interplay between tumor cells, the host cells in their proximity, and at metastatic sites [2–7]. Interactions between chemokine receptors and their respective chemokines can regulate different processes affecting the metastatic cascade, such as invasion and migration of malignant cells to distinct organs, proliferation, survival, and angiogenesis, and control of leukocyte infiltration [2, 7–14]. An elaborative understanding of chemokines-chemokine receptor biology and the mechanisms of their actions in the metastatic processes will open additional avenues for therapeutic interventions. This review highlights the role of chemokines and their receptors on distant metastasis and metastatic heterogeneity.

2 Metastasis and metastatic heterogeneity

Metastasis is a process in which tumor cells disseminate from their primary site to distant organs and establish themselves as secondary tumors or metastases in that distant organ. The metastatic process is a cascade of rate-limiting interrelated steps [15]. The development of metastatic tumor foci is the most feared and catastrophic aspect of cancer. Metastasis accounts for most cancer deaths despite advances in primary tumors' surgical resection and vigorous adjuvant therapies. There are many reasons for the failure in the treatment of metastases. Like, even before the diagnosis of primary cancer, metastases may already be present in the patient's organs. In such cases, surgical resection, radiotherapy, or chemotherapy treatment is highly unlikely due to difficulties in treating metastases because of their location and undue toxic effects of the therapeutic agent in the metastatic site. Tumor heterogeneity and therapy-resistant variants within the primary tumor and metastases are essential factors responsible for tumor therapy's refractory response.

Furthermore, interactions between tumor subpopulations and surrounding normal cells, such as metabolic cooperation, alter the sensitivity of whole tumor and metastases [16–19], compounding the problem of effective therapy for heterogeneous primary tumors and

metastatic lesions. A single anticancer drug or treatment alone offers less probability of killing a malignant tumor and its metastases. Taken together, the successful treatment of cancer patients requires the development of new approaches capable of overcoming the problem of the heterogeneous response of a primary tumor and metastases to drug treatment [20]. In the next section, we will elaborate on the factors affecting metastatic heterogeneity.

2.1 Metastatic heterogeneity

The primary tumor consists of different subpopulations of tumor cells that can differ in expression of cell surface receptors [21], such as receptors for lectins [22], hormone, synthesis of cell products [23], specialized biosynthetic enzymes [24], and metabolic characteristics [25]. These subpopulations also differ with regard to their *in vitro* and *in vivo* growth rate, based on DNA content, karyotype, and marker chromosomes [1]. Tsuruo and colleagues, in their extensive study [26], reported that this heterogeneity extends in regard to drug sensitivity among cells populating parent tumors (in vitro clones) and their metastatic subpopulations. As discussed earlier, the primary and secondary tumors' heterogeneous nature regarding cytotoxic drug sensitivity has profound implications on metastases' treatment.

2.2 Clonal cooperation

In 1939, Koch [27] isolated a metastatic subline from the Ehrlich carcinoma tumor cells, suggesting that tumors may consist of cells with differing metastatic capabilities. However, in 1977, Fidler and Kripke [28] used B16 melanoma cells to demonstrate metastatic heterogeneity within a primary tumor. Their experimental results suggested that metastatic heterogeneity is not entirely dependent on the longevity of neoplasms. Later, many studies reported that the invasive and metastatic properties of clones from the B16 melanoma tumor are highly unstable during serial passage both *in vitro* and *in vivo* [29–31]. Later, Fidler's group demonstrated that mixing and cocultivation of B16 clones dramatically reduce this metastatic instability [32]. Overall, the experimental results suggested that there is some form of "interaction" between tumor subpopulations that stabilize the subpopulations' invasive-metastatic properties and maintain their relative proportions within the tumor, preventing dominance by a few or one subpopulation. However, this "stabi1izing interaction" between subpopulations is specific for cells from the same tumor [32]. The heterogeneity in metastatic properties and metastatic instability of clones were confirmed in diverse tumors [1].

The "stabi1izing interaction" or clonal cooperation between subpopulations can also define tumors as ecosystems of interactive subpopulations [33–37]. In 1983, Miller reported that the coinjection of nonmetastatic cells with metastatic cells could increase the former's metastasis [38]. Similar cooperative heterotypic interactions were reported among EMT and non-EMT cells in prostate cancer metastasis [39] and studies proposing a leading invasive cell followed by "opportunistic" cells [40, 41].

2.3 Clonal/polyclonal origin of metastases

Metastases are the selected growth of specialized malignant cells that pre-exist as subpopulations within the parent tumor and are not a result of random survival of cells.

However, this does not answer many fundamental questions, such as whether embolus released from the primary tumor originated from a single cell or a cellular aggregate comprising of tumor cells and host cells? Whether such cellular aggregate are homotypic or heterotypic? Do metastases originate from a single progenitor or multiple progenitor tumor cells? Fidler and Hart reported that metastases result from the proliferation of a single viable cell or a single cell within a homogenous/heterogeneous aggregate. Their study further demonstrated that the circulating embolus of tumor cells is likely to be homogeneous because of a clonal zone of a primary neoplasm [42]. Also, collective migration of tumor cells into the lymphatics or vasculature plays a significant role [40, 41, 43]. Circulating cellular aggregates, whether homotypic or heterotypic, are arrested more frequently in the encountered capillary beds and demonstrate a better survival rate [44]. Circulating cell emboli consisting of tumor cells, leukocytes, and platelets offer protection against host effector cells, turbulence within the circulation. They enable to complete the metastatic cascade to the tumor progenitor cells.

In 1982, using a metastatic variant of the K-1735 melanoma cells, Talmadge et al. demonstrated that different metastases could originate from different progenitor cells. Still, most metastases appear to be clonal in origin [45]. The multiple progenitors could explain the existence of biological heterogeneity among various metastases [42]. Although not definitive, literature dominates with studies suggesting the clonal nature of metastases using different approaches to address this question· [1]. However, in 1981, Poste et al. demonstrated that metastasis cells demonstrate a high spontaneously mutation rate [32] compared to non-metastatic tumorigenic cells; thus, clonal metastases may rapidly become heterogeneous. Recent studies utilizing next-generation sequencing analysis of primary and metastatic lesions show considerable diverse results in the mutational profile sustained in metastasis, showing both high and low complexity of mutational profile. Yet, analysis of genetic mutations through large-scale genomic sequencing efforts cannot explain the basic of metastatic growths [46, 47]. In the current view, the accumulation of somatic mutation in metastasis does not drive the development of metastasis beyond the driver mutations selected for primary tumor formation [43].

Recent studies examining circulating tumor cells (CTCs) report heterogeneous cell population [48–50], suggesting polyclonal seeding of metastases. In addition, CTC clusters have a higher metastatic potential comparison with single CTCs [51]. Moreover, recent studies using lineage tracing using fluorescence markers, barcode sequencing, and whole-genome sequencing have demonstrated a mostly polyclonal nature of metastasis [52–54]. In summary, CTCs are heterogeneous with the interaction between subclones, resulting in metastatic outgrowth (polyclonal or monoclonal). However, polyclonal metastasis suggests that different heterotypic interactions among clonal subpopulations initiate metastasis.

3 Chemokines and their receptors

The word chemokine originates from the Greek word “kinos,” meaning movement. As their name suggests, they can induce directed movement in the responsive cells. Chemokines, a family of low molecular weight cytokines, were discovered in the late 1980s and early 1990s based on leukocyte chemoattractant activity upon stimulation with proinflammatory agents

[55]. Yoshimura discovered chemokine CCL2, one of the initially characterized chemokines, potent in the accumulation and activation of monocytes/macrophages during inflammation and cancer, which follows the identification of CXCL8 chemokine endowed with a potent chemotactic activity for neutrophils towards acute inflammatory responses.

Generally, chemokines are 8–15 kDa in size and structurally classified into four subfamilies (CXC, CC, C, and CX3C) [56, 57]. This structural classification's foundation is the number and location of four conserved cysteine amino acid residues linked by disulfide bonds at the N-terminus of the chemokine ligands. Biologically, chemokines function by binding to G protein–coupled receptors (GPCR) [56, 58, 59], with their N-terminus outside the cell and C-terminus with serine and threonine phosphorylation sites in the cytoplasm. GPCRs have seven-transmembrane structural loops coupled to G protein for signal transduction. Upon specific ligand binding, chemokine receptors trigger a flux in intracellular calcium ions (calcium signaling), leading to chemotaxis and the onset of cell trafficking to the desired location. Each chemokine receptor binds to one of the four chemokine subfamilies. Thus, there is a similar classification of four subfamilies of the chemokine receptors as of their respective ligands. The classical family of chemokine receptors currently has four members [60]. Apart from the above-described conventional chemokine receptors, there are atypical chemokine receptors (ACKRs), the new and emerging class of regulators of the chemokine system. Although structurally related to conventional chemokine receptors, ACKRs fail to trigger classical chemokine receptor signaling upon chemokine binding. They can also regulate the activity of canonical chemokine receptors by sharing the ligands and forming heterodimers. ACKRs can also control the bioavailability of chemokines by scavenging, transportation, or storage. ACKRs have an anti-inflammatory role and regulate growth, survival, and metastatic processes in tumor cells [61, 62].

Functionally, chemokines and their receptors can be homeostatic and inflammatory. However, some chemokines and their receptors have both homeostatic and inflammatory functionalities. One of the remarkable features of chemokines or GPCRs is their overlapping activities or one chemokine's ability to bind and activate more than one GPCR. Similarly, one GPCR may recognize more than one chemokine. This feature of "promiscuity of chemokine and their receptors" [63] endows them with an ability to compensate for another ligand during complex responses. Thus, chemokines and their GPCRs are redundant in activity, and the regulation of chemokine activities is complex. However, recent studies indicate that each chemokine or receptor has unique functionality under different physiological conditions [55]. The expression of chemokine receptors is not limited to leukocytes, but many non-leukocytic cell types express them. Similarly, chemokines/chemokine receptors can trigger diverse cellular migratory responses such as directed and undirected motility, such as haptokinesis, haptotaxis, and chemokinesis, including inducing cell adhesion and cell arrest [64].

Another essential feature of chemokines biology is their ability to undergo post-translational modification by interaction with the extracellular matrix (ECM) or tethering to "ACKR" [64]. Before we discuss chemokine' functional role in cancer biology in detail, let us discuss some salient features of different chemokine families. The CXC subfamily or α-chemokine comprises members containing one non-conserved amino acid (denoted as X) between the

first and second cysteine residues. Some CXC family chemokines have Glu-Leu-Arg (ELR) motif located at the N-terminus before the first cysteine amino acid residue [65]. This ELR motif is associated with whether the chemokine is angiogenic or angiostatic [66, 67] in nature. Thus, this family is further subdivided into two groups based on the presence or absence of an ELR motif [57, 58, 68]. The ELR^+ chemokines are potent promoters of angiogenesis, display chemotaxis for endothelial cells, and recruit neutrophils, known for their synthesis and storage of angiogenic molecules [67, 69–72]. However, ELR^- members potent inhibitors of angiogenesis [66, 72] and are known to recruit T and B cells. The CXC chemokines bind to the CXC receptor family comprising of six members.

The CC chemokine subfamily or β-chemokines comprise members with adjacent cysteine residues. The CC subfamily represents the largest sub-family of chemokines. Their family members display a diverse range of target cell specificities such as T cells, B cells, basophils, eosinophils, dendritic cells, mast cells, natural killer cells, monocytes, and macrophages [73–81]. The CC chemokines bind to the CC receptor family comprising of ten members. The majority of discovered chemokines and their respective receptors belong to the CC and CXC chemokine subfamilies.

The third group of chemokine family is the C chemokines or γ chemokines comprising of only two members with one cysteine residues on the N-terminus. These chemokines were initially described as lymphocyte-specific with XCL1 (lymphotactin-α) [82] and XCL2 (lymphotactin-β) as members. Their only chemokine receptor XCR1 was recently expressed on subsets of dendritic cells with the function of antigen cross-presentation [83].

The CX3C chemokine (δ-chemokines) subfamily contains a member CX3CL1 (Fractalkine) with three non-conserved amino acids between the first two cysteines [84]. CX3CL1 is a membrane-bound chemokine [85] shown to induce both the migration and the adhesion of leukocytes [64, 86, 87]. Table 1 summarizes the list of chemokine receptors along with their interacting ligands in humans and mice. The table also contains their expression summary in different tumor types, stromal, and immune cells.

Apart from the chemokine family mentioned above, leukotrienes, the biologically active eicosanoid lipid mediators, can act similarly to chemokines by critically modulating leukocyte migration. Leukotrienes are primarily synthesized by myeloid cells and have recently been shown to contribute to the inflammatory tumor microenvironment, resistance to immunotherapy, and metastasis [157, 158].

The chemokine system plays a pivotal role in cancer biology. Chemokines and their receptors can affect both the tumor cells and tumor microenvironment to enhance the selection of metastatic cells and eventually metastasis from the primary tumor. Various studies delineate chemokines' role in enhancing cancer cell properties, such as chemokines supporting tumor growth and proliferation, epithelial to mesenchymal transition, cancer stem cell properties, and chemotherapy resistance. Similarly, chemokines modify the tumor progression and metastasis through leukocyte recruitment, stromal interactions, angiogenesis, and creating metastatic niches. The following section will delineate the

general mechanisms (Fig. 1) by which these multifaceted chemokines intricately function and regulate metastatic progression.

3.1 Chemokines and organotropism

Organotropism or organ-specific metastasis, the non-random distribution of cancer cells among distant organs, is regulated by multiple factors, including the organ's anatomical location, blood circulation pattern, and tumor-intrinsic factor organ-specific niches, and the interaction between tumor cells and the microenvironment of the metastatic sites. As discussed earlier, chemokines are equipped with chemo-attractive signaling that can regulate leukocyte trafficking to distant organ sites. Cancer cells and endothelial cells that express the chemokine receptor migrate towards their paired chemokine gradient at non-random organ-specific sites [87, 157–159]. Thus, it is logical to expect that chemokines would have been among the first genes shown to control metastasis' molecular wheel [159]. Initial evidence showed that different cancer cells have aberrant expression of chemokine receptors, selective but not random. [160]. In 2001, Muller et al. were among the initial few groups to demonstrate chemokines' role in organ-specific metastasis. The group revealed that CCR7 and CXCR4 expression on breast cancer cells influences the invasion and organ specificity of breast cancer metastasis [160] to preferred sites positive for CCL21 (ligand for CCR7) and CXCL12 (ligand for CXCR4) expression such as the lung, liver, and bone. However, breast cancer cells' tendency to metastasize to the lung and brain is primarily determined by the vascular anatomy. Similarly, vascular anatomy dictates colorectal cancer's tendency to metastasize to the liver. Thus, some organs are more susceptible to tumor metastasis in the body, such as the lung, brain, liver, lymph nodes, and bone marrow, while other organs such as the kidneys, pancreas, and skin are less prone [161].

Studies show that chemokine receptors in cancer cells enhance invasion and metastasis and define the cancer cell's metastatic destination. A non-metastatic B16 melanoma cell line with no endogenous expression of Ccr7 metastasized to the lymph nodes on transfection with Ccr7 [162]. Similarly, CCR7 expression on a lung metastatic cell line showed metastasis to the lymph node [163]. Similarly, Cxcr4 expression on B16 melanoma cells induced metastasis to the lung [164]. In addition, microarray studies showed a very small number of differentially expressed genes on comparing primary tumors with corresponding metastases obtained from the same patient. Chemokine receptor genes are part of those differentially expressed gene pools and determine different tumors' metastatic destinations [165–167].

The characteristics of neoplastic cells and the specific microenvironment of the secondary organ can influence the site of metastasis [15]. Since chemokines can guide cells with appropriate receptors to particular locations, metastatic cancer cells can hijack the chemokine receptor system to facilitate cellular migration to trigger metastasis at distant sites [161]. Such as breast and prostate cancers are the primary cancers that metastasize to bone [168]. Multiple cancer type/subtype-specific mechanistic axes exist for bone metastasis. However, CXCL12/CXCR4-mediated chemotaxis is shared among different cancer types [161]. Along the same lines, various resident cells in the lungs secrete CXCL12 and CCL21, directing breast cancer (CXCR4) and melanoma cells (CCR7) to the lung [160].

One specific axis is the CCR9 expression in a subset of patients with melanoma tumors that shows metastasis to a rare metastatic site—the intestine (positive for the paired CCL25 expression) [149, 169].

3.2 Chemokines and their receptors on leukocyte recruitment and activation in malignant tumors

The tumor cells' intrinsic properties and different cells constituting the tumor milieu determine chemokines' expression pattern and their receptor in tissue and dictate the frequency and type of leukocyte infiltrates within the specific microenvironment [7, 170–172]. These chemokine gradients and the recruited leukocytes infiltrate population changes under pathological and inflammatory stimuli and can critically modulate tumorigenesis and metastasis. In summary, firstly, the type of chemokine present in the microenvironment and secondly, the specific receptors expressed on the infiltrating cells are the deciding factor for the number and type of infiltrated leukocytes in primary tumors and secondary tumors.

A bilateral interaction occurs between tumor cells and infiltrating leukocytes at a different stage of tumor progression. The infiltrating leukocytes can synthesize cytokines, enzymes, and different growth inhibitory/stimulatory factors such as matrix metalloproteinases (MMPs), growth, and angiogenic factors [173–177] to initiate, maintain, or terminate tumor growth and metastasis [178, 179]. Apart from primary tumors, infiltrating leukocytes can also regulate metastatic secondary tumors by balancing stimulatory (immunosuppressive factors, tumor survival, or angiogenic factors) and inhibitory activities (potent cellular immune response) by interacting with different stromal cells in the metastatic microenvironment [180, 181].

To delineate one such chemokine network, CC chemokines is a well-known network for accumulating macrophages and lymphocytes at tumor sites [182, 183]. CC chemokines can preferentially recruit macrophages and T lymphocytes, NK cells, and dendritic cells into the tumors [7, 8]. Such stromal cells' recruitment can promote tumor angiogenesis, cancer cell invasion, and/or disrupt immune surveillance and progression of the metastatic cascade [184–186]. Tumor-associated macrophages (TAMs) are one of the most abundant stromal cell types in solid tumors [187], and a high number of TAMs in the tumor correlates with poor overall survival in cancer patients [188–191]. Apart from TAM recruitment to primary tumors, such cells recruited to the metastatic sites are called metastasis-associated macrophages (MAMs) [138]. TAMs can protect cancer cells from antitumor immune reactions by directly suppressing T cell responses [192] and NK cell cytotoxicity [193, 194] through the expression of regulatory molecules such as arginase-1(ARG1), IL-10, and transforming growth factor-β (TGF-β). Therefore, the strategy to block the recruitment of TAMs and MAMs can improve the outcome of metastatic disease [195].

CCL2, initially considered a monocyte-specific chemokine, is essential in phytohemagglutinin (PHA)-stimulated leukocyte culture responsible for chemotaxis of T cell with a memory phenotype ($CD45RA^+$, $CD45RO^+$, $CD29^+$, $L\text{-selectin}^+$) [196]. Although monocytes respond to CCL2 within an hour, it requires at least 4 h to initiate a significant T cell response to CCL2. These data signify CCL2 as the link between monocytes and lymphocytes infiltration in the inflammatory sites. CCL2 involvement in T cell recruitment

leads to further investigation of T cell analogous chemotactic response to other CC chemokines such as CCL7 [197–200]. Additionally, CCL2 receptor CCR2 can regulate the migration of IL-17-producing cells, promoting inflammation in autoimmune diseases [201] as well as cancer [202] that can suppress the adaptive immune response [203]. Recently, utilizing multiple murine tumors and metastasis models, Tu [204] et al. demonstrated that CCR2 inhibition combined with anti-PD-1 enhances tumor response to immune checkpoint therapy.

The chemokine ligands/receptor axes regulating spatiotemporal recruitment, retention, and MAM expression's phenotype include CCL2-CCR2 [205] and CCL3- CCR1/CCR5 [138]. It is noteworthy to understand that upregulation of chemokines such as CCL2, CCL5, and CCL18 cannot only recruit monocytes/macrophages but also induce de novo synthesis of CCL3, CCL8, and CCL22 chemokines to reinforce the accumulation of metastasis-promoting immune cells such Treg cells as well as MAMs [138]. Monocyte-derived macrophages can secrete CCL18 to promote the secretion of Treg cells' chemokines, including CCL2, CCL3, and CCL22 [206]. Similarly, MAMs in the metastatic lung predominantly express CCL8 to recruit Treg cells mediated through receptor CCR5 [207]. Also, CCL3 was identified as the principal mediator of the communication between the neoplastic epithelium and the peripheral tissues such as lung and brain in breast cancer–bearing mice. CCL3-induced monocyte chemoattractive protein chemokines cluster with CCL7, CCL8, CCL11, and CCL12 chemokines in the distant peripheral tissues [208].

Depletion of MAMs can reduce the metastatic tumor burden of breast cancer cells in mice [209, 210]. A few functional possibilities for these observations include a recent study demonstrating that similar to TAMs, MAMs can also protect cancer cells from tumoricidal immune reactions in the metastatic sites by suppressing cytotoxicity of $CD8^+$ T cells [211]. CCL5 chemokine can prevent MAMs from becoming tumoricidal cells. Furthermore, a recent study suggests that monocytes' recruitment and subsequent accumulation of MAMs are critical for circulating breast cancer cells to establish metastases [212].

Also, the CXC chemokine network deserves mention in the process of metastasis which is involved in the recruitment of neutrophils to primary and secondary tumors. Emerging evidence indicates that heterogeneous neutrophils with plastic sub-populations are actively involved in metastasis [91, 213, 214]. In brief, several studies now suggest that CXC chemokines/receptors mediate the accumulation of neutrophils in the pre-metastatic niche [98, 215–217].

Extensive studies on tumor-infiltrating leukocytes and lymphocytes suggest depressed functionalities of these immune cells against the tumor cells [173, 218, 219]. If these depressed functionalities of macrophages/lymphocytes or any other immune population are a cytokine defect, rather than an inherent defective immune population, then manipulating chemokines and their receptors may enhance antitumor responses [220, 221]. The extent of macrophage and lymphocyte infiltration into tumors of the same histological origin can vary widely. These cells are located predominantly at the tumor and host cellular interface and represent a potential target for therapy based on immune manipulation [222, 223].

The mechanism(s) of leukocytic recruitment and activation and the significance of this process in tumor growth, heterogeneity, and metastasis are intensely investigated [5, 11]. Recent reports rationalize that tumor-infiltrating immune cells provide selection pressure that can shape tumor heterogeneity, and high heterogeneity tumors are associated with less immune response and cell infiltration [224, 225]. However, a better understanding of "cross-talk" between the malignant tumor cell and different infiltrating leukocyte populations is essential before implementing therapeutic strategies. Similarly, the relationship between the type of therapy, patient prognosis, chemokine-receptor expression, and leukocyte infiltration remains poorly understood. Thus, the development of novel adjuvant therapies requires us to delineate the interrelations between the type of therapeutic approach resulting in leukocytic infiltration, their chemokine-receptor expression pattern, and the prognosis of cancer patients.

3.3 Chemokines and their receptor in tumor angiogenesis

Assembly of new vascular structures, neovascularization, is relatively quiescent under normal adult physiological conditions and is limited to wound healing and the female reproductive processes in adults [226–229]. However, a number of diseases, including cancer, can result in abnormal neovascularization. Angiogenesis is the primary process of adult pathological neovascularization [226–229], with vasculogenesis' limited contribution [230]. Angiogenesis in tumors addresses sustenance from nutrients, oxygen supply, excretion of metabolic wastes, and carbon dioxide [231]. Angiogenesis is regulated by many angiogenic factors, metabolites such as carbohydrates, and lipids, enzymes, and members of the chemokine superfamily [67, 232].

Chemokine networks play essential roles in tumor angiogenesis [67] by the promotion or suppression of angiogenic factors such as VEGF and bFGF [67, 233, 234] in either a direct, parallel, or serial manner, proliferation [234–237], and migration [238, 239] of endothelial cells and through the recruitment of immune cells that support or inhibit angiogenesis to the tumor microenvironment [67, 238, 240, 241]. Specific chemokine members can act as pro-angiogenic molecules [67, 238], while others can be angiostatic [70, 232]. In addition, chemokines can also exert their angiogenic activity by upregulating metal metalloproteases such as MMP-2 and MMP-9 endothelial and tumor cells [242–244]. In turn, MMPs can degrade the extracellular matrix leading to endothelial cell migration, re-organization, and favoring angiogenesis [245].

The "angiogenic switch" or initiation of tumor angiogenesis is critical for tumor progression and metastasis [246]. Thus, tumor microvessel density is one of the most vital lines of evidence linking angiogenesis and metastasis. The correlation between tumor microvessel density and increased metastatic potential is present in all forms of cancers [247]. Notably, at the metastatic site, malignant tumor cells must proliferate and again undergo angiogenesis to result in a clinically relevant secondary tumor or macrometastases. Angiogenesis is essential for the growth of micrometastases. Thus, researchers propose that normal vessels' cooption can be a mechanism for metastasis vascularization [248] or contribution of bone marrow–derived endothelial progenitor cells to early angiogenic stages metastatic growth [249].

Hypoxia can serve as a link between angiogenesis and tumor heterogeneity [250]. Two prime reasons result in a hypoxic tumor microenvironment. Firstly, with cancer cells' proliferation, the inner core cells get away from the blood supply and turn hypoxic [247]. In turn, hypoxia upregulates the expression of many angiogenic growth factors in cancer cells [251–253]. Secondly, unlike normal blood vessels, tumor-associated capillaries are notoriously abnormal, tortuous, malformed, hyperplastic, and misguided. High expression of factors such as VEGF, TAMS, and angiogenic chemokines renders tumor vessels highly permeable and leaky in the tumor and metastatic environment [254]. Such irregularities in the tumor vascular network with leaky and compressed vessels make the network inefficient with poor blood flow and oxygen delivery. Low oxygenation or hypoxia can mediate cancer progression and metastasis and immunosuppression, therapy resistance, and particularly tumor heterogeneity [250].

Other than hypoxia, spatial and temporal heterogeneity of angiogenic molecules present within a single tumor and even between different metastases in a single organ [255] can result in the generation of multiple cancer cell subpopulations within the tumor and metastatic microenvironment. To exemplify, small tumors (3–4 mm in diameter) express more basic fibroblast growth factor (bFGF) and CXCL8, whereas large tumors (>10 mm in diameter) express more vascular endothelial growth factor (VEGF). On the same lines, immunostaining revealed high expression of bFGF and CXCL8 on the periphery of a large tumor and increased VEGF expression in the tumor center [256]. Similarly, matrix metalloproteinase-9 was overexpressed at the periphery of the tumor, characterized by rapidly dividing cells with VEGF expression which was localized in the center of the lesions [257]. Gradient expression of such angiogenic molecules can influence the nearby tumor cells resulting in subpopulations with differences in angiogenic potential, invasiveness, and metastatic capabilities [256, 258].

Among all the chemokines, CXCL8 is extensively studied as a potent mediator of angiogenesis. The pro-angiogenic activity of CXCL8 *in vivo* was confirmed by using the rat mesenteric window assay, the rat and rabbit corneal assay, and a subcutaneous sponge model [259–261]. Human recombinant CXCL8 was angiogenic when implanted in the rat cornea and induced proliferation and chemotaxis of human umbilical vein endothelial cells. [259] In addition, the angiogenic properties of conditioned media from activated monocytes and macrophages were attenuated by CXCL8 anti-sense oligonucleotides [259]. Furthermore, it was shown that CXCL8 could act directly on vascular endothelial cells by promoting their survival [262]. Studies from our lab and other groups suggest that CXCL8 stimulates both endothelial proliferation and capillary tube formation *in vitro* in a dose-dependent manner. These effects can be blocked by monoclonal CXCL8 antibodies [263]. In addition, CXCL8 was shown to inhibit apoptosis of endothelial cells [243]. Also, CXCL8 exerts its angiogenic activity by upregulating MMP-2 and MMP-9 in tumor and endothelial cells [242, 244]. Degradation of the extracellular matrix by MMPs is required for endothelial cell migration, organization, and, hence, angiogenesis [245]. Our group and others have demonstrated that CXCL8 directly enhances endothelial cell proliferation, survival, and MMP expression in CXCR1- and CXCR2-expressing endothelial cells, thus, may be an important player in the process of angiogenesis [74, 89, 264, 265].

CXC chemokines also include angiostatic members known to inhibit neovascularization [70, 232, 264, 266, 267]. The following examples briefly describe the angiostatic role of CXC chemokines: CXCL10 has been demonstrated to inhibit CXCL8- and FGF-2-induced angiogenesis [258]. Delivery, injection, or genetic manipulation of CXCL9 or CXCL10 expression into tumors has been shown to suppress tumor angiogenesis [268–270]. Also, intratumoral delivery of immunotherapeutic agents correlates with increased expression of CXCL9 and/or CXCL10 [271, 272]. Cell cycle–dependent expression of CXCR3 on endothelial cells mediates the angiostatic activity of CXCL9–11 [273]. Intratumoral expression of CXCL9 and CXCL10 results in decreased renal carcinoma tumor size in patients enrolled in clinical studies [274]. Interestingly, the presence of angiogenic and angiostatic CXC chemokine suggests that different chemokines' relative expression/activities in the tumor microenvironment may affect tumor angiogenesis.

A plethora of recent studies now suggest that non ELR^+ CXC chemokines and chemokine family other than CXC are also angiogenic. CC chemokines are now part of the growing list of angiogenic modulators and find implications in disease with inflammation-driven angiogenesis [237]. Initially, CC chemokines were shown to indirectly promote angiogenesis by first recruiting macrophages that release cytokines and growth factors necessary for forming a neovessel [275–277]. However, recent reports suggest CC chemokines' direct action on endothelial cells leading to enhanced vascularity [278]. For example, CC chemokines can increase nitric oxide production and endothelial cell proliferation and migration, ultimately leading to increased angiogenesis [279, 280]. Stimulation of these can also increase VEGF production to further augment neovascularization [232, 266]. A wide variety of cells, including endothelial cells, smooth muscle cells, and inflammatory cells, can secrete CC chemokines under the inflammatory stimulus [281]. Additionally, CCL2 is associated with the increase of MMP14, essential for endothelial cell migration and neovessel formation [280]. CCL2 can also recruit endothelial progenitor cells to accelerate the endothelialization process [282]. Apart from CCL2 [279], CCL1 [283], CCL11 [237], CCL15 [284], and CCL16 [285] can initiate *in vitro* endothelial tubule formation.

Another interesting chemokine modulating angiogenesis is Fractalkine (FKN, CX3CL1), a CX3C chemokine family member. CX3CL1-CX3CR1 can regulate angiogenesis in primary tumors of the breast [286], liver [287], lung [288], melanoma [289], and multiple myeloma [290]. CX3CL1-CX3CR1 can also regulate angiogenesis in two ways, by recruitment of pro-angiogenic TAM [286, 291], and by directly acting on endothelial cells resulting in their proliferation, migration, and tube formation [292–294]. Apart from contributing to cancer angiogenesis, the CX3L1-CX3CR1 axis facilitates angiogenesis in inflammatory disease. CX3L1-CX3CR1 contributes to the pathogenesis of atherosclerosis [295, 296] by promoting leukocyte adhesion to endothelial cells [86, 87] and participates in rheumatoid arthritis through endothelial cell activation [297–299].

A biological imbalance in angiogenic and angiostatic chemokine production can contribute to several angiogenesis-dependent disorders such as cancer, rheumatoid arthritis, and psoriasis [89, 265, 300–304]. How a multitude of angiogenic and angiostatic chemokines function together, whether their functionality is gradient dependent and whether a synergistic effect exists of their action on different stromal players in primary tumor and

metastases in regulating the cancer cell heterogeneous subpopulations is not clear. More studies are needed to define the contribution of tumor angiogenesis towards metastatic heterogeneity clearly. With an understanding of current literature, one can suggest a shift in the balance of expression of these angiogenic and angiostatic chemokines in favor of angiostasis by the pharmacological intervention of the specific expression chemokine check tumor and metastatic heterogeneity.

3.4 Chemokines and their receptors in epithelial to mesenchymal plasticity

Epithelial to mesenchymal transition (EMT) is a well-studied process for the process of embryonic development. Cancer cells are known to hijack such embryonic development processes like EMT [305] to enhance their dynamic state that offers numerous advantages to these cells for undergoing successful metastasis [306–309]. Cancer cells can exist in partial or intermediate plasticity with the acquired property of stemness [310]. Thus, EMT converges two hallmark properties of metastatic cells—invasiveness and stemness. Apart from the known role in cell invasiveness, EMT is emerging to contribute to stemness, immune escape, and resistance to therapy, and, most importantly, cancer cell phenotypic heterogeneity in primary tumors and metastasis [311, 312]. Chemokines and their receptors are emerging players of cancer cell EMT.

The signals activated by ligand CXCL8 through CXCR1/2 receptors result in a few well-investigated downstream signaling pathways that are linked to phenotypic plasticity [313, 314]. With a direct mechanism of action, enhanced secretion of CXCL8 in cancer cells that underwent EMT plays a role in acquiring and maintaining this plasticity, acting in an autocrine manner [315]. CXCL8 can also act in a paracrine manner on adjacent cancer cells to induce a mesenchymal phenotype. While serving indirectly, CXCL8 can activate endothelial cells or create neutrophil infiltration into the tumor site. Activation of endothelial cells results in angiogenesis [316], while neutrophils in TME can secrete additional factors, furthermore promoting EMT in the cancer cells [317, 318]. Apart from independent mechanistic actions of CXCL8, Cheng et al. in 2014 demonstrated that chemokine CCL20 could synergize with CXCL8 to bring collaborative induction of the epithelial-mesenchymal transition in colorectal cancer cells [319].

Another upcoming axis of chemokine/receptor player in EMT is CCR7/CCL21 that has implications of inducing EMT in different cancer cells such as breast [320], lung [321], oral squamous cell carcinoma [322], and pancreas [323]. This upregulation of EMT associated with the CCR7/CCL21 axis can also enhance stemness in cancers such as oral squamous cell carcinoma [322] and pancreatic carcinoma [323]. Lastly, chemokines such as CCL20 [319, 324] and CXCL5 [325, 326], and receptors such as CXCR2 [325–327] and CXCR4 [328], have been associated with bringing EMT in different cancer cells.

3.5 Chemokines and their receptors in cancer stem cell concept

As described earlier, genetic and phenotypic heterogeneity is a significant challenge in cancer management. EMP and cancer stemness are two interlinked axes that can account for cancer cells' non-genetic phenotypic plasticity [312]. Max Askanazy, a pathologist by profession, came forward with the cancer stem cell concept stating that differentiated

ovarian teratomas are derived from a single multipotent cell type [329]. With decades of research, scientists elucidated cancer cells' ability to initiate heterogeneous tumors and a relevant explanation for metastasis mirroring heterogeneity of primary tumor with cancer stem cell concept (CSC) [310]. The current CSC models state that CSC needs not to be a rare minority of tumor cells with a fixed population but dynamic. Normal stem cells need not originate CSC; the reprogrammed somatic cell can give rise to a malignant CSC, and finally, these cells can be proliferative, not quiescent. With this redefinition, tumor-initiating cells (TICs) and metastasis initiating cells (MICs), cancer cells capable of giving rise to overt secondary growth in a distant organ, are CSCs by nature [306]. The origin of MICs is elusive, with the question of whether these cells arise in the primary tumor or during the metastatic journey or at a secondary site on interaction with stromal components. Still, importantly MICs must possess the ability to survive metastatic cascade.

As stated earlier, the role of chemokines and their receptors expands beyond cellular motility and also finds relevance in maintaining cancer stem cells [5]. The chemokine/receptor axis of CXCR4-CXCL12, one of the most well-defined chemokine/receptor players, is emerging as an important player in maintaining CSC. The evidence came from high levels of CXCR4 expression in $CD44^+/CD133^+$ prostate cancer stem cells (CSCs) [330]. In this study, Dubrovska et al. demonstrated that increased CXCR4 expression on $CD44^+/CD133^+$ prostate cancer CSC promotes adhesion to the extracellular protein fibronectin and their proliferation with activation of the PI3K pathway in a CXCL12-dependent manner. The combined facilitated adhesion and proliferation by CXCR4/CXCL12 are essential for initiating secondary tumors in distant organs.

Moreover, both a CXCR4 receptor antagonist (AMD3100) and antibody could decrease tumor size and these prostate cancer progenitor cells' population. Additional evidence supporting cancer stemness linked with CXCR4/CXCL12 axis in prostate cancer came from the reports of Jung et al. showing CXCL12 expression results in the development of aggressive metastatic castration-resistant prostate cancer through induction of cancer stemness and neuroendocrine phenotypes [331]. Similarly, in breast cancer, the co-culture of the cancer cells with breast cancer–associated fibroblasts enhanced CXCL12 secretion, resulting in high spheroid formation with an enriched population of CSCs [332]. Another supporting evidence came from a study showing that CXCR4 expression enhances breast cancer cells' ability to form tumor mammospheres [122]. Lastly, elaborative research conducted in the luminal-A subtype of breast carcinoma showed that overexpression of CXCL12 elevated the proportion of CD44+/$CD24^-$ ALDH-expressing cells along with stemness markers such as sox2, Oct4, and Nanog [333].

Another chemokine receptor axis playing a significant role in promoting CSC enrichment is CXCR1/CXCR2 receptors in conjunction with CXCL1 and CXCL8 chemokines. One of the pioneer studies reported the role of CXCL8/CXCR1 in breast cancer CSCs by isolating and characterizing CSC populations in 33 cell lines using expression analysis of aldehyde dehydrogenase [334]. Gene expression profiling of these isolated aldehyde dehydrogenase positive CSCs identified a 413-gene signature that included CXCL8/CXCR1. Functionally, recombinant CXCL8 increased mammosphere formation and the ALDEFLUOR-positive population in breast cancer cell lines. Later, an elegant study from Ginestier et al.

demonstrated that blockade of CXCR1 using either a CXCR1-specific blocking antibody or repertaxin, a small-molecule CXCR1 inhibitor, selectively depleted the aldehyde dehydrogenase positive breast cancer CSC population. In their *in vivo* studies, CXCR1 blockade induced massive apoptosis in the bulk tumor population via FASL/FAS signaling and decreased metastasis at distant organs [335]. In 2013, Singh et al. delineated that the mammosphere-promoting effect of CXCL8 is partly mediated through Src and EGFR/HER2-dependent pathways. Thus, a combination of CXCR1/2 inhibitors and HER2-targeted therapies has the potential to reduce breast CSC activity [336]. In addition to the role of CXCL8 chemokine in CSCs, CXCL1-chemokine partner of CXCR2, secreted from TAMs, is reported to enhance tumor spheroids and CSC subpopulation in human TNBC cells [337]. Chen et al. observed similar results in pancreatic carcinoma that overexpression of CXCL8 self-renews pancreatic CSC through CXCR1 [338]. Apart from the CXCR4/CXCL12 and CXCR1/2/-CXCL1/8 axes mentioned above, other chemokines are also shown to generate CSCs in breast cancer such as CCL2, [339], CCL5, [340], CCR5 [341], and CXCR7/ACKR3 [342].

3.6 Chemokines and their receptors and therapy resistance

Cancer being a dynamic disease, tumors become more heterogeneous over time—heterogeneity results in spatial or temporal distinct tumor-cell subpopulations within a tumor [343]. With high levels of heterogeneity in a tumor comes differential drug sensitivity levels to treatment and inferior therapeutic outcomes. Also, selective pressure of a drug treatment can expand pre-existing subclonal drug-tolerant populations, leading to drug treatment resistance. In summary, heterogeneity is the powerhouse for drug resistance; and an evaluation of tumor heterogeneity is required for effective drug treatment in primary and secondary tumors.

On the other hand, chemotherapy resistance is often intertwined with the metastasis process. Various clinical observations such as higher frequency of metastatic tumors observed in chemoresistant primary tumors, low chemotherapy response rate in metastatic settings, and a correlation between poor chemotherapy sensitivity and metastatic occurrence [344] supports this interlink. These observations also suggest that gain of chemoresistance in tumors may select MIC cells [306]. One possible mechanism for this interlink is that chemotherapeutic treatment's toxicity results in the secretion of proinflammatory cytokines/chemokines and bioactive lipids by tumor and cells of tumor microenvironment termed as cytokine storm [345]. This pool of secreted chemokines such as CXCL12, CCL2, CCL4, and others is related to the process of metastasis through inflammation [345]. Other important mechanisms benefiting both the gain of chemoresistance and generation of MICs are CSC-like features like enhanced DNA damage response [346], detoxifying enzymes such as ALDH [347], and effective drug efflux pumps [348] as well as EMP [349, 350].

Various *in vitro* and *in vivo* studies [351–355] provide evidence that CXCR1/CXCR2 and their CXCL1/CXCL8 ligand axes can directly promote chemoresistance in breast cancer. This study also demonstrated that chemotherapy treatment, along with CXCR1/CXCR2 inhibition, reduces primary tumor burden, metastasis, angiogenesis, and therapy resistance [351–356]. CXCL8/CXCR2 also connects chemoresistance to metastasis through

CSCs, EMP, or immune infiltration in breast tumor settings [357–359]. To delineate this axis, Samantha et al. showed that reactive oxygen species generated by chemotherapy treatment induce the production of CXCL8 through activation of the hypoxia-inducible factor. Induced CXCL8, in turn, elevated tumor spheroids and ALDH-expressing cells under the chemotherapy settings [360]. Later in support of these observations, a study showed that treatment of mice with CXCR1/2 inhibitor reparixin decreased the number of tumor-initiating cells elevated under chemotherapy administration [361]. We also demonstrated that doxorubicin- and paclitaxel-resistant breast cancer cells had upregulated CXCR2 ligands, stem cell, and mesenchymal markers with higher metastatic capability in comparison with parent cells [357]. Furthermore, tumors derived from these resistant cells had higher infiltration of neutrophils and T helper 17 cells with increased IL-17 receptor, CXCR2, and CXCR2 ligands within the metastatic lungs [358]. We also demonstrated that chemotherapy resistance induced IL-17 increased CXCR2 ligands cells' expression and enhanced neutrophil chemotaxis in CXCR2-dependent manner. Lastly, the therapy-resistant breast cancer cells enhanced the secretion of pro-tumorigenic MMP9 in neutrophils [359].

In 2012, Massagués and colleagues uncovered a mechanistically defined molecular interlink between metastasis and chemoresistance in breast cancer [362]. The group demonstrated that paracrine signaling of CXCL1/2 interconnects cancer cells with stromal cells like endothelial and myeloid cells to drive both metastasis and chemoresistance processes. In brief, chemotherapeutic agents trigger TNF-α production by endothelial and other stromal cells to upregulate the CXCL1/2 expression in cancer cells. Secreted CXCL1/2 attracts $CD11b^{+}Gr1^{+}$ myeloid cells into the tumor and creates a proinflammatory environment in the lungs. Infiltrated myeloid cells produce S100A8/9 to enhance cancer cell survival in primary breast tumors and secondary lung tumors. Inhibition of CXCR2 can break the CXCL1/2-S100A8/9 loop to improve chemotherapy response and decreases metastatic burden.

Another chemokine receptor family member shown to play a role in breast cancer's chemoresistance is CXCR4 [363, 364] and CCR5 [341]. Importantly, CXCL12/CXCR4 axis also offers resistance to endocrine therapy by activating both ERα [365] and ERβ estrogen receptors in the presence of tamoxifen treatment [364, 366]. Similarly, CXCR7/ACKR3 can stabilize ERα estrogen receptor and render tamoxifen treatment in luminal-A breast cancer cells insensitive [367]. Apart from the delineated role of CXC-chemokine/receptor in chemoresistance, recent reports suggest that the CC-chemokines subfamily offers chemoresistance to the platinum drugs cisplatin, carboplatin, and oxaliplatin treatments in different cancer [368].

3.7 Chemokines and their receptors in cell survival, proliferation, and senescence

For the successful establishment of metastases, cellular survival and proliferation signals are needed at various metastatic cascade stages. For example, during dissemination, detachment of cancer cells from ECM may induce anoikis. Also, cancer cells may encounter apoptotic death signals on entering the new environment present at the metastatic sites, and lastly, cancer cells need to proliferate to establish distant metastases. Another important phenomenon is exiting from metastatic dormancy characterized by growth arrest and

survival [369]. Furthermore, dormancy reactivation requires intrinsic and extrinsic signals, a specialized microenvironment, and an immune escape [186, 370, 371].

Evidence for chemokines and chemokine receptors regulating survival and proliferation comes from various reports demonstrating the regulation of tumor growth or inhibition by chemokines through activation of different signaling pathways. One of the first indications came from chemokines CXCL1 and CXCL8, enhancing the proliferation of different melanoma cells [372–375]. Other CXC families of chemokines are involved in many cancers, including CXCL12 [376–380], CXCL2, and CXCL3 [381]. Similarly, overexpression of CXC receptors such as CXCR4 [379, 382], CXCR2 [96, 383–385], and CXCR6 [386, 387] can enhance tumor growth and progression of many cancers. Altogether, numerous reports demonstrate that CXC chemokines derived from different cellular sources [388, 389], whether acting in an autocrine or paracrine manner or alone or in synchrony with other growth regulators such as IL-6 [390], can enhance cancer cell proliferation, colonization at metastatic sites, and anchorage-independent cell growth [391] and lowers cancer cell apoptosis [392] and dormancy [393] and cell cycle arrest [351]. Various reports demonstrate increased breast cancer cell proliferation under hormonal stimulation mediated through chemokines such as CXCL12 acting through either CXCR4 or CXCR7/ACKR3 [366, 394–396].

Similarly, the CC family of chemokines and receptors can promote proliferation and provide growth-stimulating regulatory modes of tumor cells in different tumors [388, 397–402]. However, chemokine receptors in this family inhibit tumor cells' proliferation, such as CCR1 expression in human hepatocellular carcinoma cells [403]. In contrast to cellular survival, chemokines can also regulate cellular senescence. Senescence can be defined as the process in which cells undergo permanent proliferation arrest and cannot enter the cell cycle [404, 405]. However, such senescent cells are not metabolically arrested and can secrete many pro-inflammatory factors, including CXCL8 [405, 406], termed as senescence-associated secretory phenotype (SASP). Thus, senescent cells have two contradictory properties, growth arrest and proinflammatory SASP, leading to their dual role in tumor biology [407]. Senescence mediated through chemokines has been shown to promote metastasis by governing leukocytes entering the organ site [408, 409], creation of metastasis-promoting TME [410], induction of EMT [411], promoting tumor cell invasiveness [412, 413], and inducing collective invasion of the cancer cells enhancing the survival of non-senescent cancer cells [414].

3.8 Chemokine network: the link between metastatic heterogeneity and metastatic niches

Distant organs are characterized by hostile environments for the CTCs that will eventually undergo anoikis, apoptosis, or cell death due to many factors such as the absence of survival signals, energy metabolites, or incompatible stromal interactions in the host tissue [186, 415]. So, does primary tumor reeducate, corrupt, or influence this distant hostile environment to initiate metastases? A growing body of literature suggested that cancer cells and the distant organ's stroma evolve together to initiate metastasis [184, 416, 417]. Cancer cells in the primary tumor can systemically recruit stromal cells to a distant site to prepare the metastasis milieu even before the occurrence of metastatic colonization. The

conditioning continues even after the establishment of metastases [418]. This preparation leads to pre-metastatic niche formation that undergoes continuous cellular and molecular changes to prepare fertile soil for metastatic seeding.

In 2005, the group led by Dr. Lyden pioneered the research on a pre-metastatic niche [419]. By definition, a pre-metastatic niche is a supportive or receptive microenvironment for metastatic overgrowth of specialized cancer cells in a distant secondary organ, regulated by primary tumor factors such as secreted cytokines, exosomes, and mobilization of bone marrow–derived cells (BMDCs) [418–422]. Even after 15 years, this field still attracts more focus and attention [423–427]. Summarizing the understanding of current literature, we can assign specific characteristics to a pre-metastatic niche such as inflammation, organotropism, immune escape, angiogenesis, and the cascade of anchorage, survival, and proliferation [425, 426]. Chemokines are the well-established molecular hallmark of inflammation.

Additionally, we have already discussed organotropism, immune infiltration, angiogenesis, and interlink of anchorage, survival, and proliferation under the light of chemokines/receptors. Thus, chemokines and their network can orchestrate each characteristic of the metastatic niche. Moreover, we have also discussed the role of chemokines in EMP, CSCs, and therapy resistance, significant processes contributing to metastatic heterogeneity. Thus, there is an overlap between metastatic niches' characteristics and the chemokine-regulated processes contributing to metastatic heterogeneity (Fig. 2). Summarizing the overall idea, chemokine/receptor biology is the link between metastatic heterogeneity and metastatic niches. Thereby, the creation of metastatic niches at the distant organ site to support secondary tumors may also indirectly facilitate the seeding of different metastatically capable clones to survive in the new microenvironment resulting in the heterogeneous nature of metastases.

3.9 Challenges for clinical implications

Yet, there is no clinically available anti-metastatic therapy; thus, the community of cancer researchers is engaged on a current mission to find effective ways of treating and preventing metastatic tumor spread. Recent studies are unveiling the layers of a complex interaction between tumor cells and the host cell, the understanding required for effective inhibition of metastasis.

Several chemokine receptor inhibitors are under evaluation in preclinical studies and clinical trials to treat different primary tumors and metastasis (Table 2). In preclinical settings, chemokine receptor inhibitors showed promising results in reducing metastatic burden when used in combination with chemotherapy or immune checkpoint therapy. The following are brief details of clinical trials blocking chemokine/chemokine receptors in patients with a metastatic burden. Based on the preclinical evidence of a reduction in metastasis [469–471], blocking of both CCL2 and CCR2 was evaluated in clinical trials of metastatic castration–resistant prostate cancer patients (NCT00992186) and treatment of patients with bone metastasis (NCT01015560). With the concept of blocking MDSC recruitment to tumors and the pre-metastatic niche, CXCR2 antagonists are in clinical trials for metastatic castration–resistant prostate cancer (NCT03177187) and the combination

of CXCR2 antagonist with immune checkpoint inhibitor pembrolizumab for metastatic melanoma patients (NCT03161431). Additionally, CXCR4 antagonist BL-040 is in phase II clinical trial for metastatic pancreatic cancer (NCT02907099). The CXCR4 antagonist-balixafortide, combined with eribulin chemotherapy, has completed phase I trials in HER2-negative patients with heavily pretreated and relapsed metastatic breast cancer [437].

As discussed above, several clinical trials are utilizing chemokine antagonists and inhibitors; thus, targeting chemokines and their receptors for treating metastasis is not new [14, 472] but challenging for various reasons [14]. Firstly, both tumor cells and a wide range of host cells can express chemokines/receptors. Thus, blocking a chemokines/receptors pair can lead to potential side effects, such as normal immune cells expressing the same receptor will be affected. Immune cells are required to clear residual tumor cells and to prevent the residual disease-preventing relapse. Also, administration of homeostatic dosage is required to avoid unwanted immune reactions and allergies. Secondly, chemokines/receptors' promiscuous nature increases their interaction's complexity, and inhibition or inactivation of a chemokine/receptor pair may lead to compensatory effects. Thirdly, blocking specific chemokine–chemokine receptors may not serve as effective targets in the entire metastasis process and may have a restricted therapeutic window. Similarly, chemokines' profile changes with different cancer stages, drug treatment, and chemotherapy resistance, again limiting the therapeutic window. Lastly, chemokines as therapeutic agents must target cancer cell dissemination and already-established metastases and overcome metastasis heterogeneity.

Apart from challenges associated with targeting chemokines/receptors, targeting metastatic heterogeneity is also demanding. Ideally, we should approach targeting genomic instability as a source of metastasis heterogeneity. With the multitude of genes involved and other potential heterogeneity problems involved during a clinical course, it is a more daunting task than targeting cellular heterogeneity, though targeting cellular heterogeneity has important implications for the treatment of metastases. Cells present in the primary tumor do not need to represent the tumor cells populating different metastases. The extraordinary level of cellular diversity limits a single anticancer drug's success, or a single treatment, to eliminate all cancer cells present in a malignant tumor and metastases.

Thus, new therapeutic targets or modalities should focus on the characteristics that permit malignant cells to metastasize or somehow limit the number of different cancer cell subpopulations within a tumor or slow tumor cells' potential to generate new variants. Notably, the primary tumor response towards a drug and the response of the metastatic subpopulations readout should determine the efficacy of a treatment. Using a combination of anticancer therapies, the type of combination used, the administration sequence, and the time interval between successive administrations may eliminate tumor cells' different subpopulations.

4 Conclusion and future directions

Dysregulation of chemokines/chemokine receptors' biology in various tumor progression stages and metastasis is a cancer hallmark. The gain of the expression of chemokine receptors by cancer cells promotes their "specific" metastasis to organs that are positive

for the expression of the respective ligand. In their literature review of homeostatic chemokine receptors [159], Zlotnik et al. suggested a model that chemokines/receptors present on normal or cancer cells constitute a cellular highway guiding these cells to specific organs and account for a non-random metastatic destination. Moreover, primary tumors and metastases should be viewed as multi-chemokine organs, with chemokine expression dependent on the factors such as temporal/spatial localization of the chemokine source, the amount of chemokine production, whether the source of chemokine is at the tumor site or metastatic organ, and the type of cell expressing the corresponding receptors such as cancer cell, leukocytes, endothelial cells, and stromal cells. All these factors will govern which chemokine/receptor will dominate the malignancy. Identifying the specific networks of chemokines/receptors present on tumor cells and their interaction with tumor milieu opens a broad avenue for the treatment of metastasis. Furthermore, deciphering molecular mechanisms of chemokines regulating tumor phenotypes affecting metastasis will identify the cellular and molecular targets helpful in designing effective molecular targeted therapeutics.

In the last three decades, chemokine/receptor biology has made extensive progress. New chemokines/chemokine receptors were identified, characterized, and delineated their role in different biological processes like angiogenesis, tumorigenesis, host defense, immune surveillance, and the creation of metastatic niches. Many antagonists of chemokine receptors are under investigation in various clinical trials for different cancer. However, it is crucial to understand that clinical trials on chronic inflammatory diseases such as rheumatoid arthritis, AIDS, and others have not yielded significant results by targeting a single chemokine/receptor [13]. Hence, the current understanding of chemokine biology suggests exploration of chemokine/receptor antagonists in combination with currently used chemotherapeutic drugs or targeting multiple pairs of chemokine/receptors to treat metastasis. Besides, the expression of various chemokines and their receptors is associated with survival analysis of different cancer patients; thus, in the future, expression of chemokines/receptors can become a prognostic biomarker. Chemokine/receptor expression can also be included in “molecular signatures” that can determine tumor aggressiveness, select appropriate treatments for cancer patients, and respond to chemotherapy drugs.

Another future approach for treating cancer and metastasis is to take advantage of the “immune infiltration” property of chemokines. Induction of chemokines that mount an antitumor immune response in the tumor microenvironment through viral delivery of chemokines, nanoparticle delivery, or reactivating epigenetic blocks that lowers antitumor chemokines in the tumor milieu can be used as therapy [11]. However, to utilize chemokines/receptors as targets in cancer therapy, extensive research unraveling the interplay between metastatic heterogeneity and chemokine/receptor heterogeneity at the tumor and metastases is needed.

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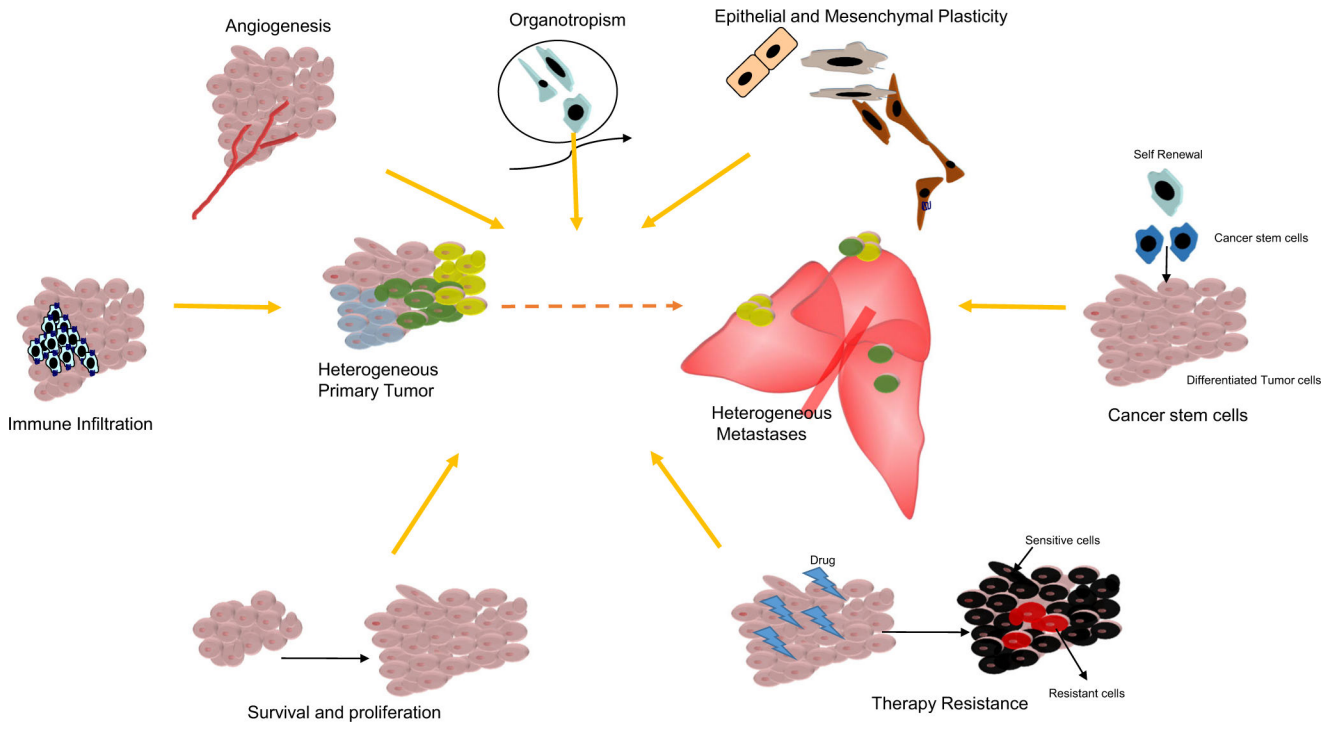

Fig. 1.

Different chemokine-regulated processes contributing to the tumor and metastatic heterogeneity. Summary of the general mechanisms by which multifaceted chemokines intricately function to regulate cancer cell properties and the tumor microenvironment to facilitate metastatic heterogeneity

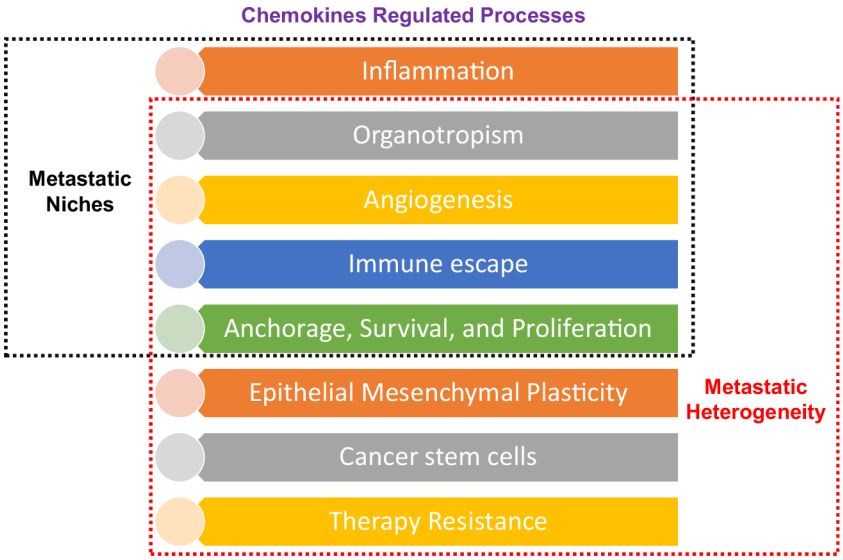

Fig. 2.

Chemokine network-the link between metastatic heterogeneity and metastatic niches. List of different chemokine regulated properties contributing to metastatic heterogeneity and creation of metastatic niches. There is an overlap between the different properties shared by these two processes, indicating metastatic niches to metastatic heterogeneity

Table 1

List of chemokine receptors and their interacting ligands in humans and mice, expression in tumor type, and different stromal/immune cells

S.no.	Chemokine receptor	Alternate name	Interacting ligand in humans	Interacting ligand in mice	Type of cancer cell	Type of stomal/immune cell
1	CXCR1	IL-8RA, CD181	CXCL1, CXCL6, CXCL7, CXCL8	CXCL1, CXCL7	Breast [88], prostrate [89], lung [89], colorectal [89], melanoma [90]	Neutrophils [91], MDSCs [92], endothelial cells [93]
2	CXCR2	IL-8RB	CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7, CXCL8	CXCL1, CXCL2, CXCL3, CXCL5, CXCL7	Breast [94], prostrate [95], lung [89], colorectal [89], melanoma [90], pancreatic [96], renal [97]	Neutrophils [91], MDSCs [98], platelets, [99], endothelial cells [93], pancreatic fibroblasts [100]
3	CXCR3	GPR9, CD183	CXCL4, CXCL9, CXCL10, CXCL11, CXCL13 [101]	CXCL4, CXCL9, CXCL10, CXCL11	Breast [102], colorectal [103], melanoma [104], leukemia [105], renal [97]	T cells [106], NKT cells [6], platelets [107]
4	CXCR4	CD184	CXCL12	CXCL12	Breast [108], prostrate [109], gastric [110], ovarian, [111], esophageal [112]	TAMs [113], endothelial [114], precursors of endothelial cells 12414810 neutrophils [115], MDSCs [116], platelets [117],
5	CXCR5	BLR1, CD185	CXCL13	CXCL13	Lymphomas [118], pancreatic [119], colon [119], head and neck [6]	B cells [120] T cells [121]
6	CXCR6	BONZO, CD186	CXCL16	CXCL16	Breast [122], prostrate [123], hepatocarcinoma [124]	Natural killer [125], natural killer T cells [124]
7	CXCR7	GPR159, ACKR3	CXCL11 [126–128], CXCL12	CXCL11, CXCL12	Breast 29257351 [127], prostrate 30952632 [129]	Endothelial 29257351 [127]
8	?		CXCL14	CXCL14		Dendritic cells 28928016 [130]
9	?			CXCL15		
10	?		CXCL17	CXCL17		
11	CCR1	CD191	CCL3, CCL4,CC-L5,CCL7,-CCL8, CCL13,CC-L14,CC-L15,CC-L16,CCL23	CCL3, CCL4,CC-L5,CCL6,-CCL7,CC-L9	(Breast, prostrate, lung, colorectal, melanoma, pancreatic, renal, cervical, hepatocellular, multiple myeloma, T cell leukemia, osteosarcoma) [131]	Neutrophils [132], platelets [133]
12	CCR2	CD192	CCL2,CC-L7,CCL8,-CCL13,CC-L16	CCL2,CC-L7,CCL12	(Breast, glioma, lung, prostrate, melanoma, multiple myeloma) [131]	TAMs, [134], MDSCs, [135], monocytes [136], platelets [133]
13	CCR3	CD193			(Breast, cervical, renal) [131]	Platelets [133]
14	CCR4	CD194, CNOT6	CCL3, CCL5, CCL17, CCL22	CCL3, CCL5, CCL17, CCL22	(T cell leukemia, Hodgkin lymphoma, breast, melanoma, hepatocellular) [131]	T cells [137], TAMs [138], platelets [133]
15	CCR5	CD195	CCL2, CCL3, CCL4, CCL5, CCL8, CCL11, CCL13, CCL14, CCl16	CCL2, CCL3, CCL4, CCL5	Breast, cervical, lung, multiple myeloma, osteosarcoma, pancreatic, prostrate [139]	TAMs [140]
16	CCR6	CD196	CCL20	CCL20	(Colorectal, breast, hepatocellular, thyroid, ovarian, cutaneous T cell, laringeal) [141]	Thl7 [142], dendritic [143]
17	CCR7	CD197	CCL19, CCL21	CCL19, CCL21	(Breast, gastric, colorectal, lung, esophageal, leukemia) [144]	Th22, Treg, T cells, [145], dendritic [146], B cells [147]

S.no.	Chemokine receptor	Alternate name	Interacting ligand in humans	Interacting ligand in mice	Type of cancer cell	Type of stomal/immune cell
18	CCR8	CD198	CCL1, CCL4, CCL16, CCL17, CCL18	CCL1, CCL8	Colon [148]	Treg [148]
19	CCR9	CD199	CCL25	CCL25	Melanoma [149], prostrate [150]	
20	CCR 10	GPR2	CCL27, CCL28	CCL27, CCL28	Melanoma [151]	
21	XCR1	GPR5	XCL1, XCL2	XCL1		Dendritic cells 28190711 [152]
22	CX3CR1	GPR13	CX3CL1	CX3CL1	Pancreatic [153], prostrate [154], breast 27001765 [155]	TAMs 32060841 [156]

Table 2

List of chemokine/chemokine receptor inhibitors tested in different tumor types in preclinical models and clinical trials. *GEM* gemcitabine, *PTX* paclitaxel, *FX* FOLFIRINOX; inhibitors in red ink are used for metastatic or relapse therapy

Tumor Type	Receptor Target	Inhibitors	Clinical Trials
Brain tumor	CXCR4	PRX177561 + Bevacizumab + Suntininib (438) POL5551 + aVGEF (439, 440) AMD3465 (441)	**USL311 + Lomustine** (NCT02765165) **AMD3100** (NCI2012–00149; NCI2013–02012)
	ACKR3	X7Ab + Temozolomide (442)	
Breast Cancer	CCR1	CCX9588 + Anti-PDL1 (443)	
	CCL2	CNTO888 + Radiotherapy (444)	
	CXCR2		**Reparixin + PTX**NCT0237038 (445)
	CXCR4		**LY2510924** (NCT02737072) (446) **Balixafortide + Erbulin**NCT01837095(374) **USL311 + Lomustine** (NCT02765165)
Colon & Gastric Cancer	CCR1	BL5923 (447)	
	CCR4	AF399/420/1802 (448)	
	CCR5		**Meraviroc + Chemotherapy**(NCT0136813) (449)
	CCR7	si RNA (450)	
	CXCR2	Reparixin + 5-fluorouracil (451)	
	CXCR4		**LY2510924**NCT02737072 (446)
Hematologic Malignancies	CCR1	CCX721 (452, 453)	
	CCR4	Anti-CCR4 CAR T-cells (454)	**Mogamulizumab** (NCT01728805) (455)
	CCR7	MSM R707 (456)	
	CXCR4	AMD3100 + Ara-C (457) BKT140 + Rituximab (458) LY2510924 (459),(458)	**PF-06747143** (NCT02954653) **AMD3100**NCT00512252 (460) **BMS936564**NCT01120457 (461)
Hepatocellularcarcinoma	CCR2	747 + Sorafenib (462) RDC018 (417)	
Lung Cancer	CCR4	AF399/420/1802 (448)	
	CXCR4	AMD3100 + VIC-008 (463)	**LY2510924**NCT02737072 (446)
Ovarian & Prostate cancer	CCR2	iCCR2 (464)	
	CCL2		**CNTO888**NCT00992186 (465, 466)
	CCR7	siRNA (450)	

Tumor Type	Receptor Target	Inhibitors	Clinical Trials
	CXCR2	SB225002 + Sorafenib (467)	NCT03177187
		SB265610 + Docetaxel (468)	
	CXCR4	AMD3100 (469)	**LY2510924**NCT02737072 (446)
Pancreatic cancer	CCR2	PF-04136309 + GEM (470) CCX872 + Anti-PD1 (471)	**PF-04136309 + nab-PTX + GEM**NCT02732938 (472) **PF-04136309 + FX**NCT01413022 (473) **CCX872 + FX**NCT02345408 (474)
	CXCR2	$CXCR2^{-/-}$ (475) $CXCR2^{-/-}$ + Anti-PD1 (149) SB225002 + RS504393 + FX (475)	**AZD5069**NCT02583477
	CXCR4	AMD3100 + Anti-PDL1 (476)	**BL-040** (NCT02907099)
Renal Carcinoma	CCR4	Affi5 (477)	
Skin tumor	CCR4	AF399/420/1802 (448)	
	CXCR2	Navarixin + Anti-MEK (476)	NCT03161431